REMARKS / ARGUMENTS

The Office Action mailed February 12, 2006 has been received and reviewed. Claims 1 through 20 were pending in the Application, and claims 7 through 9, 12 and 15 through 20 were withdrawn from consideration as being directed to a non-elected invention. Claims 1 through 6, 10, 11, 13 and 14 were rejected. Claims 1 through 6, 10, 11 and 13 have been amended as shown above.

In the Specification, the paragraph that begins on line 8 of page 65, and the paragraph that begins on line 21 of page 44 have been amended to remove the embedded hyperlinks objected to by the Examiner.

Applicants hereby respectfully request reconsideration of the amended Application, and offer the following remarks / arguments for consideration by the examiner.

AMENDMENTS TO THE SPECIFICATION

The paragraph that begins on line 8 of page 65, and the paragraph that begins on line 21 of page 44, are being amended to remove embedded Uniform Resource Locator hypertext code, and replace the code with physical addresses where the information or materials can be obtained. These amendments should be entered into the record, because they add no new matter to the Application and require no additional search by the Examiner.

AMENDMENTS TO THE CLAIMS

Claims 1 through 6, 10, 11 and 13 are being amended as shown above, in order to address the concerns of the Examiner, improve the clarity of the claims, correct grammatical or typographic errors, and remove subject matter related to a non-elected aspect of the present invention. These amendments are fully supported by the as-filed Specification, as explained below, and should also be entered into the record because they also do not add any new matter to the Application, and they do not necessitate any additional search of the claimed subject matter. These amendments, in the context of the outstanding rejections, will be discussed below.

OBJECTIONS TO THE SPECIFICATION

As noted above, the paragraph of the Specification that begins on line 8 of page 65, and the paragraph that begins on line 21 of page 44, have been amended to remove embedded Uniform Resource Locator hypertext code, and replace the code with physical addresses where the information or materials can be obtained. These amendments remove all embedded Uniform Resource Locator hypertext code from the Specification and thereby obviate the Examiner's objection.

THE REJECTIONS

Claim Rejections under 35 USC § 112, 2nd paragraph

Claims 3-6, 10 and 13-14 have been rejected under 35 USC § 112, 2nd paragraph for allegedly being indefinite and failing to point out and distinctly claim the subject matter which applicants regard as the invention. The rejection under 35 USC § 112, 2nd paragraph is in two parts. In the first part, the Examiner alleges that meaning of "C373T" is unclear, since the claims "provide no reference point in any sequence to determine what constitutes position 373...," and she rejects Claims 3, 10 and 13 based upon this conclusion. In the second part, the Examiner has identified a grammatical error that raises issues of proper antecedent basis of Claim 6, and she rejects this claim for that reason. These two aspects of the rejection will now be address independently.

The meaning of "C373T:"

With regard to the first part of the rejection, Applicants first note that definiteness of a claim must be analyzed, not in a vacuum, but in light of: (A) The content of the particular Application disclosure; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See M.P.E.P. §2173.02 (8th Ed. Rev. 2) May 2004, p. 2100-205. The intent of the definiteness requirement is to provide a notice function by clearly warning others as to what constitutes infringement. *Solomon v. Kimberly Clark*, 216 F.3d 1372, 1379 (Fed. Cir. 2000). Where the language of the claim makes the metes and bounds of the invention clear, breadth is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689 (CCPA 1971).

Applicants respectfully assert that in issuing the rejection under 35 USC § 112, 2nd paragraph, the Examiner has not fully taken into consideration the content of the as-filed Application disclosure, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made, particularly with regard to what is disclosed in the as-filed Sequence Listing and Figure 1. In an effort to highlight particular aspects of the as-filed Application disclosure, and thereby familiarize the Examiner with claimed invention, Applicants offer the following discussion.

DESCRIPTION OF SEQUENCES PROVIDED IN THE SEQUENCE LISTING, SPECIFIC PASSAGES FROM THE SPECIFICATION THAT AID IN THE UNDERSTANDING OF THE CLAIMED INVENTION, AND THE MEANING OF "C373T"

The instant Application was filed with a 98-page "Informal Sequence Listing" which not only provided nucleotide and amino acid sequences relevant to the invention, but also provided descriptive information for each of the sequences listed. This descriptive information has been extracted from the as-filed Informal Sequence Listing, and is being provided herewith, in *Exhibit A*, for use by the Examiner in understanding the present invention, and reviewing the contents of the instant Application and its formal Sequence Listing.

Also, the Application, as filed, provides additional teachings within its Specification regarding the contents of the formal Sequence Listing, as regards the claimed invention. Of particular note are the following passages.

"The inventors have discovered that a number of splice variants of TBC1D1 exist, each of which is encoded by a unique combination of exons that are spliced together to form the TBC1D1 coding sequence (CDS). **The most common form of the TBC1D1 CDS is provided as SEQ ID NO:1.** The corresponding amino acid sequence is set forth in SEQ ID NO:2." (Specification; p. 5, ll. 16-20; emphasis added.)

"In addition, mutant cDNAs bearing germline mutations in their CDSs have also been isolated. The sequences of the CDSs of these mutant transcripts are shown in SEQ ID NOs:15, 17, 19 and 21, and the amino acid sequences encoded by the CDSs are shown

in SEQ ID NOs:16, 18, 20 and 22, respectively. **The mutation found in disequilibrium with obesity and provided in SEQ ID NO:15 is C373T, which corresponds to an amino acid variant R125W, provided in SEQ ID NO:16.**" (Specification; p. 5, ll. 20-25; emphasis added.)

"Based on cDNA cloning and sequence analysis, a large number of exons of *TBC1D1* have been found. These exons can be alternatively spliced to create several different splice variants, as described below. **The nucleotide sequences of the individual exons encoding portions of all known forms of TBC1D1 are provided** in SEQ ID NOs:33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, and 80.. **Exon 1 encodes a portion of the *TBC1D1* transcript 5'-UTR, as well as the first 139 amino acid residues from the N-terminus of TBC1D1.** The portion of the 5' UTR encoded by exon 1 corresponds to that found just upstream (5') of the translation initiation codon – **a portion present in all known *TBC1D1* transcripts.**" (Specification; p. 6, ll. 3-11; emphasis added.)

"*TBC1D1* transcripts have been found to contain one of two alternative 5'-UTRs. The 5'-most regions of these alternative 5'-UTRs correspond to either of the sequences encoded by one of two nontranslated exons, designated exon 22 (SEQ ID NO:79) and exon 23 (SEQ ID NO:80). **To create a full-length cDNA transcript, exon 22 or exon 23 is spliced to the 5' end of the first coding exon – exon 1 (SEQ ID NO:33) – to form cDNAs containing coding sequences corresponding to any of the CDS structures diagramed in Figure 1.** Importantly, exons 22 and 23 are separated by 3 kilobasepairs in the genomic DNA (SEQ ID NO:28) and therefore are derived from separate promoters. It is likely that these promoters comprise important regulatory elements that impart tissue and/or temporal specificity to the distribution of *TBC1D1* transcripts." (Specification; p. 6, ll. 20-29; emphasis added.)

In addition to these specific passages in the as-filed specification, the following additional aspects of the as-filed disclosure should be noted by the Examiner:

1. "Figure 1 is a schematic diagram showing the exon structures of various alternatively spliced forms of **TBC1D1 coding sequence. The sequences of the exons identified by numbers in the figure are provided in the sequence listing.**" (Specification; p. 5, ll. 5-7; emphasis added.)

2. The names given to the coding exons depicted in Figure 1 are used throughout the Application. Note that the first coding exon is named exon "1," but, for historical reasons, the second coding exon is named exon "3.1," etc.
3. SEQ ID NO:33 provides the nucleotide sequence of exon "1," the first coding exon, but, as noted above, "exon 1 encodes a portion of the *TBC1D1* transcript 5'-UTR, as well as the first 139 amino acid residues from the N-terminus of TBC1D1."

4. Figure 1 shows that exon "1" – the first coding exon – is present in all known alternative *TBC1D1* transcripts, including the most abundant transcript (labeled "A" in Figure 1, the sequence of which is provided as SEQ ID NO:1 in the Sequence Listing.

5. The nucleotide sequence of genomic DNA comprising all known TBC1D1 exons (both coding and non-coding) is provided as SEQ ID NO:28 in the Sequence Listing.

In view of the aspects of the disclosure outlined above, Applicants respectfully assert that it would be clear to a skilled artisan that nucleotide variant identified by the term "C373T," which is disclosed as corresponding to the amino acid variant R125W, means a nucleotide substitution occurring at the 373rd nucleotide of the TBC1D1 coding sequence, wherein a cytidine is replaced by a thymidine. By virtue of the location of this nucleotide substitution (at the 373rd nucleotide of the coding sequence) it would also be clear to a skilled artisan that the substitution occurs at the first nucleotide within the 125th codon of the TBC1D1 coding sequence, which comprises the 373rd, 374th and 375th nucleotides in the coding sequence. Inspection of these three nucleotide positions in the coding sequence provided by SEQ ID NO:1, and comparison to the equivalent nucleotides provided in SEQ ID NO:15 reveals that the C373T substitution mutation results in the conversion of an arginine codon (CGG) to a tryptophan codon (TGG), which, as indicated in the Specification, corresponds to amino acid variant R125W.

Applicants further assert that a skilled artisan, in view of the disclosures outlined above, when provided with the exemplary (and most abundant) TBC1D1 coding sequence of SEQ ID NO:1, and the nucleotide sequence of the first coding exon as SEQ

ID NO:33, would readily recognize and understand that the C373T substitution mutation occurring within the context of the coding sequence of the first coding exon, corresponds to the nucleotide change "C466T" within the context of the full nucleotide sequence of exon 1 provided as SEQ ID NO:33, since alignment and comparison of these two sequences would reveal that the initiation codon comprising the first three nucleotides of SEQ ID NO:1, comprises nucleotides 93, 94 and 95 of SEQ ID NO:33.

In view of these assertions, the content of the as-filed Application disclosure, and the claim interpretation that would be given by one possessing an ordinary level of skill in the pertinent art at the time the invention was made, and in further view of the Examiner's concerns for clarity, Applicants have amended Claims 3, 10 and 13 to better define the claimed nucleotide variants with reference to specific reference sequences. Applicants believe that these amendments remove any uncertainty as to the location and nature of the TBC1D1 nucleotide variants associated with an increased risk of obesity. Consequently, Applicants believe that amended Claims 3, 10 and 13 particularly point out and distinctly claim the subject matter which Applicants regard as their invention, and ask that the rejection of Claims 3-5, 10 and 13-14 under 35 USC § 112, 2nd paragraph, be withdrawn.

Improper antecedent basis of the word "alterations" in claim 6:

With regard to the rejection based upon an alleged lack of antecedent basis of the term "alterations" in Claim 6, Applicants have amended Claim 6 to replace the plural "alterations" with the singular "alteration," thereby correcting the grammatical error identified by the Examiner that gave rise to the rejection of lack of proper antecedent basis in the claim.

In light of the above amendments and arguments, Applicants respectfully assert that the present claims meet the definiteness requirement under 35 USC § 112, 2nd paragraph, and request that the rejection of Claim 3-6, 10 and 13-14, under 35 USC § 112, 2nd paragraph, be withdrawn.

Claim Rejections under 35 USC § 112, 1st paragraph, Written Description

Claims 1-6, 10-11, and 13-14 stand rejected under 35 USC § 112, 1st paragraph, as being based upon a disclosure that allegedly provides insufficient Written Description. The numerous aspects of this rejection will be addressed topic-by-topic, in essentially the order they were raised in the first Office Action on the merits, mailed January 12, 2006.

The Specification teaches numerous relevant nucleotide sequences, which were overlooked by the Examiner, and the meaning of "C373T" in the context of "any TBC1D1 encoding nucleic acid molecule" is clear:

First, the Office Action alleges that "[t]he specification ... does not teach the full sequence of the TBC1D1 gene, or the genomic sequences which would be considered as a "TBC1D1 encoding nucleic acid". The specification teaches that TBC1D1 has a number of splice variants (figure 1), however the sequences of all variants do not appear to be taught." (Office Action, page 6, lines 16-18).

In response to these specific allegations, Applicants refer the Examiner to *Exhibit A*, and note that the specification teaches the "full [nucleotide] sequence of the TBC1D1 gene" as SEQ ID NO:28. The specification also teaches the nucleotide sequences of all of the known exons of the *TBC1D1* gene as SEQ ID NOs:33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79 and 80. Finally, the specification teaches the nucleotide sequences of the "coding sequences" of splice variants A through P, depicted in Figure 1, as SEQ ID NOs:1, 29, 31, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103 and 105, respectively.

Second, the Office Action alleges that the meaning of "C373T" in the context of "any TBC1D1 encoding nucleic acid molecule" is unclear. Applicants respectfully submit that in view of the discussion provided in the previous section of this response, one of average skill in the art, apprised of the complete disclosure of the pending application, including the Sequence Listing provided at the time of filing, would understand exactly what is meant by of "C373T" in the context of "any TBC1D1 encoding nucleic acid molecule."

With respect to those aspect of the Written Description rejection that pertain to nucleotide and/or amino acid sequences, Applicants respectfully suggest that much of the

rejection appears to have resulted from incomplete understanding of what has been disclosed in the Specification and it's accompanying Sequence Listing, by the Examiner. For purpose of clarification, and for future reference, Applicants note the following:

1. The specification teaches several splice variants of TBC1D1, each of which is encoded by a unique combination of exons spliced together to form the TBC1D1 coding sequence (CDS), as depicted in Figure 1. While a large number of TBC1D1 splice variants exist, the specification teaches that "[t]he most common form of the TBC1D1 CDS is provided as SEQ ID NO:1. The corresponding amino acid sequence is set forth in SEQ ID NO:2." (Specification, page 5, lines 18-20.)
2. Inspection of SEQ ID NO:1 reveals that it begins with an "ATG" initiation codon, ends with a "TGA" stop codon, and comprises 3,507 nucleotides, or the equivalent of 1,169 codons, including the TGA stop codon.
3. Inspection of SEQ ID NO:2 reveals that it comprises 1,168 amino acids, encoded by the first 1,168 codons of SEQ ID NO:1, and that it begins with a methionine residue and ends with an aspartate residue.
4. The specification teaches that mutant cDNAs bearing germline mutations in their CDSs were isolated, and that: "The sequences of the CDSs of these mutant transcripts are shown in SEQ ID NOs:15, 17, 19 and 21, and the amino acid sequences encoded by the CDSs are shown in SEQ ID NOs:16, 18, 20 and 22, respectively." (Specification, page 5, lines 21-23.)
5. Inspection of SEQ ID NOs:15, 17, 19 and 21 reveals that they each comprise 3,507 nucleotides, and each begin with an ATG initiation codon and end with a TGA stop codon.
6. Inspection of SEQ ID NOs:16, 18, 20 and 22 reveals that they each comprise 1,168 amino acids, beginning with a methionine residue and ending with an aspartate residue.
7. Close inspection of SEQ ID NO:15, relative to SEQ ID NO:1, reveals that it bears a thymidine at nucleotide 373, as compared to a cytidine at the same position in SEQ ID NO:1. As noted above, this "C373T" substitution / transition results in a missense mutation which encodes amino acid variant R125W, provided in SEQ ID NO:16.

8. Similarly, close inspection of SEQ ID NOs:17, 19 and 21, reveal that they correspond to the CDSs of variant TBC1D1-encoding nucleic acids bearing the T683G, C1174G and both T683G and C1174G mutations, respectively, in the context of CDSs, such as those depicted as CDS A in Figure 1.
9. Whereas, close inspection of SEQ ID NOs:18, 20 and 22, reveal that they correspond to the amino acid sequences encoded by SEQ ID NOs:17, 19 and 21, respectively.
10. The specification also teaches that: "The nucleotide sequences of the individual exons encoding portions of all known forms of TBC1D1 are provided in SEQ ID NOs:33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, and 80. Exon 1 encodes a portion of the TBC1D1 transcript 5'-UTR, as well as the first 139 amino acid residues from the N-terminus of TBC1D1. The portion of the 5' UTR encoded by exon 1 corresponds to that found just upstream (5') of the translation initiation codon – a portion present in all known TBC1D1 transcripts. (Specification, page 6, lines 5 – 11.)
11. The descriptive information provided with the Informal Sequence Listing confirms that SEQ ID NO:33 corresponds to "EXON 1 NT," whereas SEQ ID NO:34 corresponds to "EXON 1 AA." (See *Exhibit A*.)
12. Close inspection of SEQ ID NO:33 reveals that it contains an open reading frame, beginning with the adenosine at nucleotide number 94, that encodes 139 amino acid residues, wherein residue number 125 is an arginine encoded by a CGG codon, which comprises nucleotide residues equivalent to residues 373, 374 and 375 of SEQ ID NO:1.
13. The specification specifically teaches: "The term "equivalent" as used in this and other similar contexts means the equivalent nucleotide of C373T, T683G or C1174G, **relative to SEQ ID NO:1, in other variant TBC1D1 nucleic acids** (e.g., alternative spliced forms), although the exact number representing the location of the equivalent in the variant TBC1D1 nucleic acid may be different." (Specification, page 13, lines 13-17; emphasis added.)
14. Both the Informal Sequence Listing provided at the time of filing, and the Formal Sequence Listing provided subsequently, contain SEQ ID NO:28, which corresponds to 249,881 nucleotides of genomic DNA nucleotide sequence including all of the

known exons of the *TBC1D1* gene, including the exon referred to as "exon 1" (SEQ ID NO:33), which, in turn, contains the "C373" residue, that is replaced by a thymidine in individuals bearing the "C373T" substitution mutation.

15. Finally, the specification teaches: "TBC1D1 transcripts have been found to contain one of two alternative 5'-UTRs. The 5'-most regions of these alternative 5'-UTRs correspond to either of the sequences encoded by one of two nontranslated exons, designated exon 22 (SEQ ID NO:79) and exon 23 (SEQ ID NO:80). To create a full-length cDNA transcript, exon 22 or exon 23 is spliced to the 5' end of the first coding exon – exon 1 (SEQ ID NO:33) – to form cDNAs containing coding sequences corresponding to any of the CDS structures diagramed in Figure 1. Importantly, exons 22 and 23 are separated by 3 kilobasepairs in the genomic DNA (SEQ ID NO:28) and therefore are derived from separate promoters. It is likely that these promoters comprise important regulatory elements that impart tissue and/or temporal specificity to the distribution of TBC1D1 transcripts." (Specification, page 6, lines 20-29.)

Adequate Written Description is provided to support claims that encompass a large genus of diagnostic methods based upon TBC1D1-encoding nucleic acids comprising nucleotide polymorphisms:

The Office Action alleges (on page 8) that the claims "encompass a large genus of nucleic acids which comprise polymorphisms in any TBC1D1 encoding nucleic acid sequence, which are not disclosed in the specification." without disclosing "common element[s] or attributes." In response, Applicants note that while the claims do indeed encompass a large genus of nucleic acids which comprise polymorphisms in TBC1D1 encoding nucleic acid, the claims are drawn to compositions of matter (i.e., isolated nucleic acids), but instead are drawn to methods of assessing increased risk of human subjects developing obesity based upon a heretofore unknown association of mutations in the *TBC1D1* gene with this risk. Applicants note that they have provided examples of at least three nucleotide variants of the TBC1D1-encoding nucleic acids (e.g., C373T, T683G, and C1174G) that appear to be associated with an increased risk of obesity in

human subjects. The data supporting this association are presented in Example 1, pages 52-55, of the Specification.

In view of these teachings, Applicants respectfully assert that they have clearly provided sufficient written description to support claims directed to diagnostic methods that, for example, read upon determining whether a human subject is at risk for developing obesity comprising the step of determining the presence or absence of the "C373T" mutation in TBC1D1-encoding nucleic acids. Applicants further assert, that apprised of the disclosure of the instant specification, one of average skill in the art would appreciate that the inventors had discovered a much broader association between an increased risk of obesity in human subjects and specific mutations occurring within TBC1D1-encoding nucleic acids. Further, such skilled artisans would immediately appreciate that the inventors were in possession of at least three species of methods – based upon three specific mutations – for diagnosing an increased risk of obesity in human patients by identifying polymorphisms within TBC1D1-encoding nucleic acids. Applicants also assert that these three species of methods for diagnosing an increased risk of obesity in human patients by identifying polymorphisms within TBC1D1-encoding nucleic acids are sufficient to support a genus of methods directed to diagnosing an increased risk of obesity in human patients by identifying polymorphisms within TBC1D1-encoding nucleic acids.

<u>Inventors are not required to set forth how or why their invention works:</u>

On page 9, the Office Action makes the allegation "No predictable correlation between the structural alteration in the amino acid R125W variant and a risk for developing obesity is provided by the Specification. In response to this allegation, and subsequent passages of the Office Action, Applicants respectfully asserts that the Examiner appears to be suggesting that in order to provide sufficient written description for the claimed methods, the Applicants must include detailed information on the function of the TBC1D1, and how the specific polymorphisms found to be associated with obesity alter this function and contribute to the etiology of obesity in patients bearing such mutations. For example, the Office Action, on page 10, second paragraph states: "The specification provides no correlation between structure of polymorphisms

and the function of such polymorphisms with an increased risk for obesity ... The specification does not teach the function of TBC1D1 nor how it's function, or lack of function, or altered function are predictably associated with obesity."

Applicants respectfully, but vigorously object to the apparent requirement by the Examiner that the specification teach the molecular details of how mutations affect TBC1D1 function and thereby increase a patient's risk of obesity. Such a requirement is akin to requiring the Applicants to know, and describe, precisely how their invention works, and it is well-established law that an Applicant need not know, nor describe, the details of how their invention works. Specifically, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." Newman v. Quigg, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989); see also Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests.").

The Written Description Requirement is met by the disclosure of a single working embodiment of the invention:

On page 11 of the Office Action, the Examiner alleges that the Written Description Requirement has not been met, because "[i]n the instant case, the specification fails to teach the necessary common attributes or features of the genus encompassed nucleic acids and polymorphisms in view of the species disclosed."

In response, Applicants respectfully note that the United States Patent and Trademark Office (PTO) has issued guidelines for the examination of patent applications under the 35 USC § 112, first paragraph, written description requirement. These guidelines state that the written description requirement of 35 USC § 112, first paragraph, can be met by

> show[ing] that an invention is complete by disclosure of sufficiently detailed , relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Guidelines for Examination of Patent Applications under 35 USC § 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001) (emphasis added).

Applicants further note that this standard was adopted by the United States Court of Appeals for the Federal Circuit in *Enzo* at 964. In *University of Rochester v. G.D. Searle*, 358 F.3d 916 (Fed. Cir. 2004) the Federal Circuit reaffirmed its approval of *Enzo's* use of the PTO written description guidelines. Very recently, the Federal Circuit reaffirmed and applied the standard in *Invitrogen Corporation v. Clonetech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005). This latter case will now be discussed in detail.

At issue in *Invitrogen* were three patents-in-suit that each claim a genetically modified reverse transcriptase (RT) in terms of two distinct functional attributes – namely an RNA-dependent DNA polymerase ("reverse transcriptase" or RT) activity, and an RNA-DNA hybrid-specific nuclease (RNase H) activity. The disputed claims made use of these functional attributes to define the invention. Claim 1 of U.S. Patent No. 6,063,608 (the '608 patent) is representative. It reads

> 1. An isolated polypeptide having DNA polymerase activity and substantially reduced RNase H activity, wherein said polypeptide is encoded by a modified reverse transcriptase nucleotide sequence that encodes a modified amino acid sequence resulting in said polypeptide having substantially reduced RNase H activity, and wherein said nucleotide sequence is derived from an organism selected from the group consisting of a retrovirus, yeast, Neurospora, Drosophila, primates and rodents.

'608 patent, col. 19, lines 26-34 (claim 1). As noted by the Federal Circuit, "[w]ith these patents Invitrogen thereby claims a compound (the polypeptide or genetically engineered RT) in terms of biological function (DNA polymerase and RNase H activity)." *Id.* at 1072.

Close examination of the '608 patent specification reveals that while it discloses two different nucleotide sequences (one in Figure 6 and from columns 5 through 8, and one from columns 2 through 6) that potentially encode two different embodiments of the claimed invention, both of these nucleotide sequences are derived from a single source – the Maloney-Murine Leukemia Virus (M-MLV; a retrovirus) – and only the first of these

(the RT coding sequence of plasmid pRTdEcoRV-C that encodes the N-terminal-most 504 amino acid residues of M-MLV RT) was shown to encode a polypeptide having the functional features of the claimed invention. In other words, in total, the '608 patent specification provided only ONE working embodiment of an isolated RT polypeptide having DNA polymerase activity and substantially reduced RNase H activity that had been reduced to practice.

In *Invitrogen*, which was an appeal from the judgment of the United States District Court for the District of Maryland, the validity of the claims of '608 patent (and the claims of other patents-in-suit) was called into question under 35 USC § 112, first paragraph's "written description" requirement by the defendant, Clontech Laboratories, Inc. Clontech argued that *University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997) compels the conclusion that the claims-in-suit fail the written description requirement because they do not recite the DNA or protein sequences as required by *Eli Lilly*, at 1566-69, and *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993). According to Clontech, the district court erred in finding sufficient structure in the DNA sequence recited in the common specification, and within the knowledge of one of ordinary skill in the art, because the claims at issue "are not limited to sequences recited in the specification and do not recite DNA or protein sequence." *Invitrogen* 429 F.3d at 1073.

In response, the Federal Circuit ruled

> "Clontech's appeal to *Eli Lilly* and *Fiers* is misplaced. In those cases, the patent specifications at issue did not identify the sequence (structure) of **any** embodiment of DNA claimed therein. ... In contrast, the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of **a representative embodiment** of the claimed RT enzyme. The specification also discloses test data that **the** enzyme produced by **the** listed sequence **has the claimed features** – DNA polymerase activity without RNase activity. Under both the Eli Lilly and Fiers analysis, the specification at bar is sufficient.
>
> In short, ... the claims in the patents-in-suit satisfy the written description requirement of § 112."

Invitrogen, at 1073-4 (emphasis added).

In view of the Federal Circuit ruling in *Invitrogen*, Applicants respectfully submit that the instant Application clearly provides sufficient written description of the claimed invention because it recites three representative embodiments of the claimed methods for

diagnosing an increased risk of obesity in human subjects based upon the detection of genetic variants of TBC1D1-encoding nucleic acids characterized by the mutations.

Amended Claim 13 is now limited to human subjects:

On page 10, the Office Action notes that "[w]ith regard to claim 13, the claim also encompasses analysis in any individual, which encompasses non human species. However, the specification provides no predictable correlation that the polymorphism "C373T" exists in any TBC1D1 encoding nucleic acid from any species."

In response, Applicants have replaced the phrase "an individual" with the phrase "a human subject," thereby obviating this part of the Written Description rejection.

Amgen v. Chugai and Written Description in the instant Application:

Finally, the Office Action relies on *Amgen v. Chugai* to support the position that adequate written description requires "more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required." Applicants respectfully assert that this reference is misplaced. Amgen set forth a simultaneous conception/reduction rule for claims drawn to nucleic acids. Specifically, where an application claims a particular nucleic acid sequence, the nucleic acid must be known. However, the present invention is not drawn to nucleic acids, but rather to a diagnostic method based upon identifying nucleotide variations in them. Notwithstanding this, the Application provides example nucleic acids encompassing the C373T, T683G, and C1174G mutations in the context of a TBC1D1 coding sequence, as SEQ ID NO:15, 17 and 19, respectively.

In view of the amendments and arguments provided, and the recent decision by the United States Court of Appeals for the Federal Circuit in *Invitrogen v. Clontech*, Applicants respectfully assert that the invention defined by the pending claims is fully described by the disclosure in the as-filed Specification. Consequently, Applicants respectfully request the withdrawal of the written description rejection under 35 USC § 112, 1st paragraph.

Claim Rejections under 35 USC § 112, 1st paragraph, Enablement

Claims 1-6, 10-11, and 13-14 stand rejected under 35 USC § 112, 1st paragraph, as being based upon a disclosure that allegedly provides insufficient enablement.

While the written rejection and the details allegedly supporting the rejection in the First Office Action on the Merits mailed January 12, 2006, are quite voluminous – covering some six pages – the bottom line appears to be that that undue experimentation would allegedly be required for one to practice the invention commensurate in scope with the claims, because (a) the claims are "in an art whose nature is identified as unpredictable," (b) the state of the prior art provides little guidance, (c) the claims are broad, and (d) a large quantity of experimentation would be necessary to practice the claimed invention.

With respect to the enablement rejection, as applied in the instant case, Applicants note that the issue of enablement of biotechnological inventions under 35 USC § 112, first paragraph, was recently addressed by the Federal Circuit in *Invitrogen Corporation v. Clonetech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005). In *Invitrogen* the Federal Circuit affirmed that:

> **"[t]he enablement requirement is met if the description enables any mode of making and using the invention."** Johns Hopkins Univ. v. Cellpro, Inc., 152 F.3d 1342, 1361 (Fed. Cir. 1998); accord Amgen Inc. v. Hoechyst Marion Roussel, Inc., 314 F.3d 1313, 1335 (Fed. Cir. 2003); Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1533 (Fed. Cir. 1991). **In this case Invitrogen's teachings regarding deletion mutation is sufficient to satisfy its part of the patent bargain, as it fully teaches a mode of making the claimed invention."**
>
> Clonetech mistakenly relies on our decision in National Recovery to support its nonenablement argument. In National Recovery the court affirmed judgment that a patent claim was invalid for lack of enablement. 166 F.3d at 1198. The claim was to method, not a compound. The claimed method called for selecting certain signals for processing, yet the written description failed to teach one of ordinary skill in the art how to select among various candidate signals. Id. at 1196. A person of ordinary skill, reading the patent, would have been required to engage in undue experimentation before reaching **a means** of practicing the claimed method. In short, the National Recovery enablement problem **concerned a failure to disclose any way to practice the claimed method. In this case, by contrast, Invitrogen fully describes an operable method for achieving the claimed mutation.**

> **Enablement does not require the inventor to foresee every means of implementing an invention at pains of losing his patent franchise. Were it otherwise, claimed inventions would not include improved modes of practicing those inventions. Such narrow patent rights would rapidly become worthless as new modes of practicing the invention developed, and the inventor would lose the benefit of the patent bargain."**

Invitrogen at 1070-71 (emphasis added).

Applicant respectfully asserts that this recent decision of the Federal Circuit in *Invitrogen* has bearing on the instant case. In particular, Applicant asserts that the amended claims at issue in the present Application are enabled by the specification because the specification fully describes an operable embodiment of the claimed invention – a method for determining whether a human subject is at risk for developing obesity, comprising detecting:

"a cytidine to thymidine transition at the 466th nucleotide in the sense strand of the first TCB1D1 coding exon (SEQ ID NO:33), or the complement thereof;

a cytidine to thymidine transition at the 373rd nucleotide of the TCB1D1 coding sequence of SEQ ID NO:1, or the complement thereof;

a cytidine to thymidine transition at the 373rd nucleotide of the TCB1D1 coding sequence of an alternative transcript comprising the coding sequence encoded by the first TCB1D1 coding exon (SEQ ID NO:33), or the complement thereof;

or a nucleotide variant that results in an arginine to tryptophan substitution at the 125th amino acid residue of a TBC1D1 protein, or the complement thereof."

In addition, the specification also describes methods for determining whether a human subject is at risk for developing obesity, comprising detecting the T683G and C1174G variants of the *TBC1D1* gene, and their gene products, and provides extensive teachings on how such variants can be identified. Consequently, the as-filed specification fully enables multiple ways to practice the claimed method using multiple variants of the *TBC1D1* gene, and its gene products, identified by the inventors.

In view of this, Applicants assert that the disclosure provided in the specification is sufficient to satisfy the Applicant's part of the patent bargain – because it fully teaches assessing an increased risk of obesity in human subjects using least three distinct

polymorphisms of the TBC1D1 gene that the inventors have shown to be associated with an increased risk of obesity in studies of obese families.

Further, while the scope of a patent's claims must be less than or equal to the scope of the enablement, the scope of enablement, in turn, is that which is disclosed in the specification **plus the scope of what would be known to one of ordinary skill in the art without undue experimentation**. Nat'l Recovery, 166 F.3d at 1196 (Fed. Cir. 1999), emphasis added. Applicants respectfully assert that the identification of additional TBC1D1 variants associated with an increased risk of obesity can be achieved using routine experimentation, which does not rise to the level of undue experimentation. Further, Applicants assert that one of skill in the art of molecular diagnostics would readily appreciate that the real advance in the useful arts provided by the claimed invention was the discovery that nucleotide changes in the coding region of the *TBC1D1* gene are associated with an increased risk of obesity in human subjects. Apprised of this discovery, such skilled artisans could readily set about to identity other TBC1D1 variants associated with an increased risk of obesity, using routine experimentation.

In view of these arguments, and the recent decision by the United States Court of Appeals for the Federal Circuit in *Invitrogen v. Clontech*, Applicants respectfully assert that the invention defined by the pending claims is fully enabled by the disclosure in the as-filed Specification. Consequently, Applicants respectfully request the withdrawal of the enablement rejection under 35 USC § 112, 1st paragraph.

CONCLUSION

Applicants believe that once the amendments proposed above have been incorporated into the pending claims, and the arguments presented above are considered, the outstanding rejections will be withdrawn and the pending claims will be in condition for allowance, and an early notice thereof is respectfully solicited. Should the Examiner determine that additional issues remain which might be resolved by a telephone conference, she is respectfully invited to contact the undersigned via his direct line (801-883-3463).

A petition for a one-month extension of time for the filing of this response is being filed concurrently herewith. Provisions for the payment of the necessary fee have been made in the petition. Therefore, it is believed that no other extension of time, or any additional fees are due with this response. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees or deficiency or credit any over payment to Deposit Account no. **50-1627**.

Respectfully submitted,

Herbert L. Ley III, Ph.D.
Registration No. 53,215

Date: May 12, 2006

Intellectual Property Department
Myriad Genetics, Inc.
(Customer No. 26698)
320 Wakara Way
Salt Lake City, UT 84108
Telephone: 801-584-3600
Fax: 801-883-3871